European Journal of Surgical Oncology xxx (2018) 1–7

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Risk factors for the development of invasive cancer in unresected ductal carcinoma in situ

Anthony J. Maxwell [a, b, *], Karen Clements [c], Bridget Hilton [c], David J. Dodwell [d], Andrew Evans [e], Olive Kearins [c], Sarah E. Pinder [f], Jeremy Thomas [g], Matthew G. Wallis [h], Alastair M. Thompson [i], for the Sloane Project Steering Group

[a] Nightingale Centre, Wythenshawe Hospital, Manchester, M23 9LT, UK
[b] Division of Informatics, Imaging & Data Sciences, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, M13 9PT, UK
[c] Screening Quality Assurance Service (Midlands and East), Public Health England, 1st Floor, 5 St Philip's Place, Birmingham, B3 2PW, UK
[d] Nuffield Department of Population Health, University of Oxford, Richard Doll Building, Old Road Campus, Oxford, OX3 7LF, UK
[e] Ninewells Hospital and Medical School, Mailbox 4, Level 6, Dundee, DD1 9SY, UK
[f] Cancer Studies, King's College London, 9th Floor, Innovation Hub, Comprehensive Cancer Centre, Guy's Hospital, Great Maze Pond, London, SE1 9RT, UK
[g] Department of Pathology, Western General Hospital, Edinburgh, EH4 2XU, UK
[h] Cambridge Breast Unit, Cambridge University Hospitals NHS Foundation Trust, Cambridge & NIHR Cambridge Biomedical Research Centre, Cambridge, CB2 0QQ, UK
[i] Department of Breast Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, 77030, USA

ARTICLE INFO

Article history:
Accepted 26 December 2017
Available online xxx

Keywords:
DCIS
Invasion
Breast cancer
Surgery
Microcalcification
Endocrine therapy

ABSTRACT

Background: The natural history of ductal carcinoma in situ (DCIS) remains uncertain. The risk factors for the development of invasive cancer in unresected DCIS are unclear.
Methods: Women diagnosed with DCIS on needle biopsy after 1997 who did not undergo surgical resection for ≥1 year after diagnosis were identified by breast centres and the cancer registry and outcomes were reviewed.
Results: Eighty-nine women with DCIS diagnosed 1998–2010 were identified. The median age at diagnosis was 75 (range 44–94) years with median follow-up (diagnosis to death, invasive disease or last review) of 59 (12–180) months. Twenty-nine women (33%) developed invasive breast cancer after a median interval of 45 (12–144) months. 14/29 (48%) with high grade, 10/31 (32%) with intermediate grade and 3/17 (18%) with low grade DCIS developed invasive cancer after median intervals of 38, 60 and 51 months. The cumulative incidence of invasion was significantly higher in high grade DCIS than other grades ($p = .0016$, log-rank test). Invasion was more frequent in lesions with calcification as the predominant feature (23/50 v. 5/25; $p = .042$) and in younger women ($p = .0002$). Endocrine therapy was associated with a lower rate of invasive breast cancer ($p = .048$).
Conclusions: High cytonuclear grade, mammographic microcalcification, young age and lack of endocrine therapy were risk factors for DCIS progression to invasive cancer. Surgical excision of high grade DCIS remains the treatment of choice. Given the uncertain long-term natural history of non-high grade DCIS, the option of active surveillance of women with this condition should be offered within a clinical trial.

Introduction

Ductal carcinoma in situ (DCIS) is diagnosed predominantly through mammographic screening programmes and now comprises 20% or more of new breast cancers [1]. Concern has been expressed regarding possible overtreatment [2], given the excellent long term survival of women with DCIS [3,4]. Some have suggested that "nothing is better than something" [5] and proposed long-term

* Corresponding author. Nightingale Centre, Wythenshawe Hospital, Manchester, M23 9LT, UK.
E-mail addresses: anthony.maxwell@manchester.ac.uk (A.J. Maxwell), karen.clements@phe.gov.uk (K. Clements), bridget.hilton@phe.gov.uk (B. Hilton), david.dodwell@nhs.net (D.J. Dodwell), a.z.evans@dundee.ac.uk (A. Evans), olive.kearins@phe.gov.uk (O. Kearins), sarah.pinder@kcl.ac.uk (S.E. Pinder), jeremy.thomas@luht.scot.nhs.uk (J. Thomas), matthew.wallis@addenbrookes.nhs.uk (M.G. Wallis), AThompson1@mdanderson.org (A.M. Thompson).

https://doi.org/10.1016/j.ejso.2017.12.007
0748-7983/

surveillance for estrogen receptor (ER) positive DCIS [6,7]. Randomised trials comparing the outcomes of active surveillance (AS) with conventional surgery and adjuvant treatment have opened in the UK (the LORIS trial) [8], the US (the COMET trial) [9] and Europe (the LORD trial) [10]. Endocrine therapy in the AS arms is optional in COMET, optional but not encouraged in LORIS and not allowed in LORD.

While there is an historic literature describing the natural history of DCIS in small, predominantly pre-screening series of symptomatic disease [11], there is also a growing understanding that DCIS is a heterogeneous condition. It has been reported as a common incidental finding at autopsy with a median 8.9% prevalence in a review of seven studies of women who died of unrelated causes [12]. These series, conducted over 30 years ago, used variable diagnostic criteria, compounded by the difficulty of diagnosing DCIS in tissue that is likely to have been poorly preserved. The current prevalence of undiagnosed DCIS therefore remains uncertain.

Whatever the true prevalence, surgery, radiotherapy and endocrine therapy remain the mainstays of guideline-concordant care. However, some 2.0–2.3% of patients diagnosed with DCIS in the USA choose AS for management of their disease [4,13]. Without treatment, it has been estimated that only 20–30% of DCIS will progress to invasive cancer [11,14].

Furthermore, it is not known whether long-term disease outcome is adversely impacted by awaiting progression to invasive disease.

Given this background, we sought to identify women in the recent breast screening era who had not received surgical resection for histologically diagnosed DCIS and to consider risk factors and long-term outcomes for such women as a comparator for active surveillance trials.

Material and methods

The West Midlands Cancer Intelligence Unit (WMCIU, now incorporated into the National Cancer Registration and Analysis Service, part of Public Health England) and the Scottish Cancer Registry identified 2505 possible eligible patients from cancer registrations of women diagnosed in England and Scotland between 1 January 1996 and 31 December 2009

These women had a needle biopsy diagnosis of DCIS but no record of subsequent surgery. Details were sent to Lead Clinicians in each hospital following completion of a confidentiality agreement. In addition, National Health Service (NHS) Breast Units and NHS Breast Screening Programme (NHSBSP) centres in the United Kingdom were invited to submit details of known patients with DCIS diagnosed from 1 January 2010 onwards who had not undergone surgical excision for at least one year following confirmed histological diagnosis on needle biopsy. Additionally, some women diagnosed between 2003 and 2012 were identified via the NHSBSP prospective cohort study of screen-detected non-invasive neoplasias, the Sloane Project (www.sloaneproject.org.uk).

A comprehensive registration form was completed for each case by the submitting centre, including details of the imaging and clinical findings, mode of biopsy, histopathology, reasons (where known) for not performing surgery and relevant drug treatment and/or radiotherapy. A follow-up form was completed for each subsequent episode, which included one or more of clinical assessment, mammogram and ultrasound (continuing drug treatment was not formally recorded). A third form was completed for any further needle biopsy or surgery. Forms were returned to the WMCIU/Public Health England where the data were entered onto a database. Missing data on tumour characteristics together with date and cause of death were obtained from the National Cancer Registration and Analysis Service. Data were exported to an Excel spreadsheet for analysis. Registration opened in 2012 and closed in December 2016.

Statistical methods

Univariate analysis only was performed due to the relatively small size of the dataset. Comparisons of categorical data were made using Fisher's Exact test. Continuous variables were assessed by the Mann-Whitney *U* test. Cumulative incidence curves were compared using Kaplan-Meier analysis and the log rank test. Analysis was conducted using Stata version 14 (StataCorp LLC, College Station, Texas, USA).

Results

Data from 89 eligible women identified from 31 breast units were returned. In all cases the initial DCIS diagnoses were made between 1998 and 2010 (no eligible cases diagnosed after 2010 were submitted despite specific requests for such cases). The median patient age at diagnosis was 75 years (range 44–94 years). The DCIS was screen-detected in 39 women (44%) with a median age of 65 years; the remaining 50 were diagnosed through other routes (symptomatic clinics and incidental findings) and had a median age of 82 years. The median duration of follow-up (diagnosis to death, invasive disease or last review) was 59 months (range 12–180 months).

The symptoms of the 50 women who were diagnosed other than through screening are poorly documented. Three each presented with a lump, a nipple discharge and nipple changes. Clinical examination was recorded as normal in 7, benign in 3, indeterminate in 9, suspicious in 8 and malignant in 8; clinical findings were not recorded in 15. It is likely that a number of DCIS lesions were incidentally detected on mammography performed for investigation of unrelated symptoms.

Thirty-five women (39%) were recorded as being unfit for surgery (without details of the comorbidities), 37 (42%) declined surgery, four (4%) were both unfit and declined surgery, other (unspecified) reasons were stated for eight (9%) and the reasons were unknown for five (6%) patients.

Mammographic features

The predominant mammographic features were known for 75 of the 89 women. Fifty (67%) were microcalcification, granular microcalcification being the most common. Nine of the 25 women with other predominant features (mass or deformity) had microcalcification as a secondary feature. The median mammographic lesion size for women in whom both size and grade were known was 34 mm (range 8–88) for high grade DCIS (n = 23), 32 mm (5–126) for intermediate grade DCIS (n = 23) and 15 mm (4–64) for low grade DCIS (n = 11).

Needle biopsy

In 63 women, the initial DCIS diagnosis was made with 14-gauge (G) core needle biopsy (CNB). Only ten women were known to have been diagnosed with vacuum-assisted biopsy (VAB) (one each of 14G and 11G, five 10G and unknown gauge in three). In sixteen women, the biopsy technique was classed as either 'other' or unknown but were not open biopsies (12 were image-guided and one freehand; the remaining three were in women unfit for surgery). Of the 72 women where the mode of guidance was known, 37 biopsies were performed under stereotaxis, 28 ultrasound and seven

Please cite this article in press as: Maxwell AJ, et al., Risk factors for the development of invasive cancer in unresected ductal carcinoma in situ, European Journal of Surgical Oncology (2018), https://doi.org/10.1016/j.ejso.2017.12.007

freehand. No DCIS diagnoses were made solely on fine needle aspiration cytology.

Cytonuclear grade of DCIS and presence of microinvasion

The grade of the DCIS at needle biopsy was known for 77 of the 89 women. Twenty-nine were high, 31 intermediate and 17 low grade. Microinvasion was only recorded as definitely present in one woman (grade unknown) and possibly present in four (one low grade, one intermediate grade, one high grade, one grade not known). Microinvasion was specifically stated to be absent on needle biopsy in 59 and not stated (presumed absent) in 25.

Histological necrosis

The presence or absence of histological necrosis in association with the DCIS was recorded in 53 women. Of the 50 in whom both necrosis status and the primary mammographic feature were known, 9/31 with microcalcification and 4/19 with another primary radiological feature had necrosis (p = .742, Fisher exact test).

Estrogen receptor (ER) status

ER status was positive in 43 of the 48 women in whom ER was recorded (positivity was regarded as an Allred score ≥3/8 where the score was stated, otherwise as defined by the submitting centre).

Non-surgical treatment

Forty-four women were treated with endocrine therapy (ET) - 26 with an aromatase inhibitor, 17 with tamoxifen and one with each type sequentially. One woman treated with an aromatase inhibitor also received external beam radiotherapy. Thirty women treated with ET were recorded as having known ER positive DCIS. Thirty-five women received no ET; eight were known to have ER positive disease. Non-surgical treatment information was not available for 10 women.

Development of invasive cancer

Twenty-nine women (33%) had invasive breast cancer diagnosed histologically after a median interval of 45 months (range 12–144 months) following the initial DCIS diagnosis. A further five women who died had invasive breast cancer recorded as their primary cause of death on death certification but no histological confirmation of this was recorded on the cancer registry; these five were not included amongst those who developed invasive cancer for the purposes of this analysis (see discussion). The 29 women who developed proven invasive cancer were significantly younger than the 60 who did not (median ages 67 years versus 78 years respectively; $p = .0002$, Mann-Whitney *U* Test). Younger women had a similar median length of follow-up to older women (age ≤70 years v. age>70 years: 60 months v. 58 months; $p = .45$; Mann-Whitney *U* test), although there was a non-significantly higher proportion of younger women with high grade disease (39% v. 27%; $p = .26$, Fisher exact test).

One invasive cancer was recorded as having developed in the same breast but a different quadrant to the known high grade DCIS; this has been included as a case of DCIS progression for consistency with other published studies. As far as is known, the remaining 28 invasive cancers developed at the site of the DCIS.

Comparison of DCIS grade on the initial biopsy and the predominant mammographic feature for those with and without progression to invasive cancer is shown in Table 1. After median intervals of 38, 60 and 51 months respectively, 14/29 (48%) women with high grade DCIS, 10/31 (32%) with intermediate grade and 3/17 (18%) with low grade DCIS developed invasive cancer; grade was not known in 12. The cumulative incidence of invasive disease was significantly higher in women with high grade DCIS than in those with other grades ($p = .0016$, log-rank test) – Fig. 1. None of the five women with microinvasion on the initial biopsy developed invasive breast cancer. All six of the grade 3 invasive cancers occurred in women with a prior diagnosis of high grade DCIS (Table 2).

Twenty-three of the 50 (46%) women with microcalcification as the predominant radiological feature developed invasion compared to only five of the 25 (20%) with another known predominant radiological feature ($p = .042$, Fisher exact test).

Of the 53 women with known histological necrosis status, 7/14 (50%) with necrosis and 13/39 (33%) without necrosis developed invasive cancer ($p = .341$, Fisher exact test).

For those with known DCIS grade and mammographic size, no correlation between lesion size and the subsequent development of invasion was demonstrated ($p = .109$–$.921$; Mann-Whitney *U* test; data not shown).

Nine of 44 women (20%) who received endocrine therapy developed invasive cancer compared to 15 of 35 (43%) who did not ($p = .048$, Fisher exact test).

Of the 25 known women who did not have microcalcification as the predominant feature, four of the 10 (40%) with secondary microcalcification developed invasive cancer compared to one of the 15 (7%) without microcalcification ($p = .12$, Fisher exact test).

Surgery

Eighteen women ultimately underwent breast surgery, seventeen for invasive cancer: Thirteen had mastectomy and four wide local excision. One woman had a wide local excision for DCIS 12 months after initial diagnosis.

Table 1
Predominant radiological feature and cytonuclear grade of DCIS at core needle biopsy (denominators) and numbers that developed invasive cancer (numerators).

Predominant radiological feature	Low grade	Intermediate grade	High grade	Grade not known	Total	
Microcalcification - casting	0/1	3/8	3/6	1/2	7/17	Microcalcification 23/50
Microcalcification - granular	1/2	4/9	5/8	0/0	10/19	
Microcalcification - punctate	2/3	0/0	1/2	0/0	3/5	
Microcalcification - pattern not known	0/0	1/6	2/2	0/1	3/9	
Mass – ill-defined	0/1	1/1	0/1	1/1	2/4	Mass 5/18
Mass – well-defined	0/2	0/1	2/4	0/3	2/10	
Spiculate mass	0/2	0/0	1/1	0/1	1/4	
Stromal deformity	0/0	0/0	0/2	0/0	0/2	
None of the above	0/3	0/1	0/0	0/1	0/5	
Not known	0/3	1/5	0/3	0/3	1/14	
Total	3/17	10/31	14/29	2/12	29/89	

Please cite this article in press as: Maxwell AJ, et al., Risk factors for the development of invasive cancer in unresected ductal carcinoma in situ, European Journal of Surgical Oncology (2018), https://doi.org/10.1016/j.ejso.2017.12.007

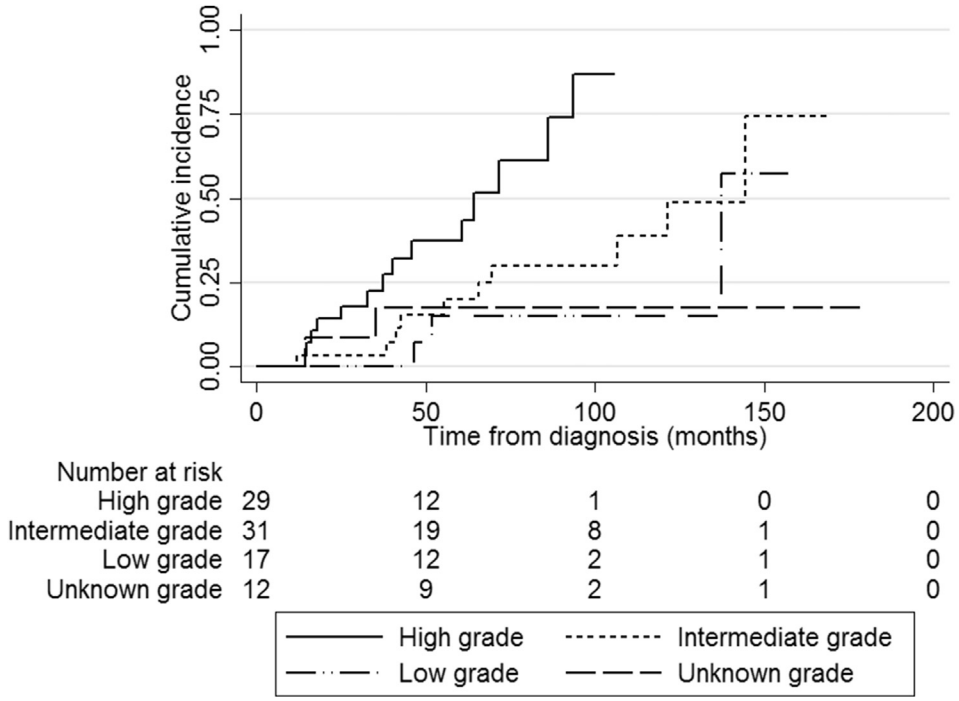

Fig. 1. Cumulative incidence of invasive cancer by DCIS grade. Kaplan-Meier chart showing the cumulative incidence of invasive cancer from time of DCIS diagnosis by cytonuclear grade of DCIS.

Table 2
Invasive carcinoma type and histological grade and the cytonuclear grade of the original DCIS, where known.

Original DCIS grade	IDC grade 1	IDC grade 2	IDC grade 3	Other invasive cancer	Not known	Total
High	0	2	6	1 invasive lobular carcinoma grade 2	5	14
Intermediate	2	3	0	1 mixed carcinoma	4	10
Low	1	1	0	0	1	3
Not known	0	0	0	1 invasive lobular carcinoma grade 2; 1 invasive papillary carcinoma	0	2
Total	3	6	6	4	10	29

IDC–Invasive ductal carcinoma.

Deaths

Forty-eight women died. Eleven of these had biopsy-proven invasive cancer, of whom seven had a primary certified cause of death of breast cancer.

For women that developed invasive cancer the median interval from diagnosis to death was 62 months for all-cause deaths and 62 months for deaths from breast cancer. For those that did not develop invasive cancer the median interval was 57 months ($p = .28$, Mann-Whitney *U* Test).

Among the 29 women with invasive cancer, there was no significant difference between the age at diagnosis of DCIS for those who died compared with the women still alive at census (median ages 68 years v. 66 years respectively; $p = .62$, Mann-Whitney *U* Test). However, of the women who did not develop invasive cancer, those who died were significantly older at diagnosis than those who remained alive (median ages 83 years v. 69 years; $p = .0001$, Mann-Whitney *U* Test).

Discussion

This retrospective longitudinal cohort study of women diagnosed with DCIS on core needle biopsy who did not undergo surgical excision for at least one year reviewed 89 eligible women. Progression to invasive breast cancer was more frequent in a short time frame for those with initial DCIS of high cytonuclear grade. The Kaplan-Meier analysis suggests that approximately 50% of women with high grade DCIS will develop invasive cancer within five years but fewer than 25% of those with lower grade DCIS will develop invasion in the same time frame. In particular, low grade DCIS appears to progress slowly to invasive cancer. For approximately one in seven of the women who died, the cause of death was attributed to breast cancer, with a median survival in these women of over five years from DCIS diagnosis.

The tendency for high grade DCIS to be associated with grade 3 invasive cancer and the significantly higher cumulative incidence of invasion suggest that the biological behaviour is reflected in the histopathological appearances of the DCIS. This effect of grade is similar to that seen for DCIS recurrence following surgical resection [15]. Our findings emphasise the importance of early detection and treatment of women with high grade DCIS in order to prevent the development of high grade invasive cancer.

Even with the confounding factor of a slightly higher proportion of high grade disease in the younger (≤70 years) women, the rate of progression to invasion does appear to be higher in younger women. This is in keeping with the known higher local recurrence rate in younger women following surgical resection of DCIS [1,16,17] and with the higher proportion of invasive recurrences seen in these women [18].

Please cite this article in press as: Maxwell AJ, et al., Risk factors for the development of invasive cancer in unresected ductal carcinoma in situ, European Journal of Surgical Oncology (2018), https://doi.org/10.1016/j.ejso.2017.12.007

The apparent association of DCIS microcalcification with the development of invasive disease has not been previously reported, although microcalcification has been shown to be associated with a higher risk of non-invasive recurrence [19]. In addition, there have been some suggestions that invasive cancers with microcalcification have a worse prognosis than non-calcified lesions [20–22], although this is not a consistent finding [23] and may be due to confounding factors [24]. Our findings are rather at variance with those of other studies which have shown a higher upstaging rate at surgery of DCIS with an associated mammographic mass [25,26], and the small number of women with masses in this study precludes further analysis of possible confounding factors.

The effect of endocrine therapy in reducing progression of DCIS to invasive cancer noted here is consistent with the findings of trials of adjuvant endocrine therapy following surgery for DCIS. The UK/ANZ DCIS trial [27] and the NSABP B-24 study [28] demonstrated a significant reduction in the frequency of DCIS recurrence with tamoxifen, although the UK/ANZ study did not show a significant reduction in invasive recurrence. Anastrozole has subsequently been demonstrated to be at least as effective as tamoxifen in this setting [29,30].

The contribution of DCIS detection at screening to reduction of breast cancer mortality has long been debated. A review of prior mammograms of women with incident screen-detected cancers suggested that undiagnosed calcified DCIS progresses to invasive cancer within the three-year period between screens in a significant number of women [31], but only recently have data been published that demonstrate that high DCIS detection rates at screening are associated with a reduction in the incidence of interval cancers [32].

Sagara et al. [4] reported outcomes of 57,222 women with DCIS from the SEER (Surveillance, Epidemiology and End Results) database, of whom 1169 (2%) had not undergone surgical resection. Although the development of invasive disease was not specifically examined, for women with high and intermediate grade DCIS there was a significant difference in 10-year breast cancer specific survival between those who underwent surgery and those who did not (98.4% v. 90.5%, $p < .001$, for high grade; 98.6% v. 94.6%, $p < .001$, for intermediate grade disease, respectively). Surgery was not, however, associated with a survival difference in women with low grade DCIS (98.6% v. 98.8%; $P = .95$). The median follow-up, however, was only six years, and further study is required to determine whether this effect persists in the longer term (cf. the discussion below about long term recurrence rates after surgery). A series following 14 women with ER positive DCIS who underwent endocrine therapy as an alternative to immediate surgery [6] reported that eight subsequently had surgery after a median follow-up of 28 months; five had with stage I invasive ductal cancers. Although there were only 17 women with low grade DCIS in the present study, eight died of non-breast cancer related causes and the findings suggest that low grade DCIS is a relatively indolent disease. Of the three women who did develop invasion after intervals of 46, 51 and 137 months, one of the invasive cancers was of histological grade 1, one grade 2 and the other was of unknown grade. These findings, together with the demonstrated lack of survival benefit from surgery [4], also support ongoing studies of active surveillance as an alternative to surgery in low risk DCIS [8–10].

To our knowledge, this is the largest study reporting the progression of histologically confirmed unresected DCIS to invasive breast cancer. Diagnostic and treatment data were obtained from clinicians managing the women, supplemented by cancer registry data, and consequently data completeness is relatively high. Although variability in the application of diagnostic and grading criteria to DCIS by histopathologists is well recognised [33], the mandatory participation in a national quality assurance programme by all UK pathologists working in breast screening [34] provides some reassurance.

This study has limitations. Despite the large number of women with a DCIS diagnosis but no record of surgery on the cancer registries (2505 (5%) potentially eligible out of a total of 49,567 DCIS registrations in the period 1996–2009), only a relatively small number of patients (0.2%) had data submitted by the treating centres, with potential for selection bias. The proportion of women diagnosed with DCIS in the UK who do not undergo surgery is, therefore, unknown, but appears similar to the 2.0–2.3% reported in the USA [4,13]. Because of the nature of the study population (with regard to patient age and associated co-morbidities), many of the women died of competing causes during the course of the study, substantially limiting the duration of follow-up. Furthermore, there were relatively few younger women with screen-detected DCIS. Given that DCIS is most commonly diagnosed through screening [35,36], the disproportionate number of women in this study with DCIS diagnosed through other routes (either symptomatic or incidentally detected on mammography performed for investigation of unrelated symptoms) is probably because screening mammography in the UK is targeted at women aged 70 years of age or younger who are more likely to be suitable for, and to be willing to undergo, primary surgical resection of DCIS than older women who were diagnosed outside the screening service.

Although endocrine treatment was recorded on the initial assessment form it was not recorded on the subsequent forms and it is possible that some women stopped treatment, or conversely that others commenced treatment.

Five women died with a primary certified cause of death of breast cancer but no corresponding cancer registration of invasive breast cancer. These have not been included as having developed invasive disease in the analysis. This is because there is known to be a high discrepancy rate in death certification, with up to a third of deaths being incorrectly certified [37], whereas the UK cancer registries (now unified as the National Cancer Registration and Analysis Service) have an ascertainment rate of around 98% [38]. It is, however, possible that the number of women who developed invasive cancer has been slightly understated.

Although the rate of development of invasive cancer in women with low grade DCIS appears to be much lower than that in women with high grade DCIS in the short term (the median follow-up was just under 5 years), it is not possible to determine the longer-term behaviour of low grade DCIS from this study. Solin et al., [39] in a study of 268 women with DCIS treated by wide local excision and radiotherapy, demonstrated that the local recurrence rate of high grade DCIS with necrosis was four times that of the other lesions at 5 years (12% v 3%) but that continued recurrences in the less aggressive group brought the rates much closer together by 10 years (18% v. 15%). A similar but less marked effect was seen in the Early Breast Cancer Trialists' Collaborative Group overview of randomised radiotherapy trials in DCIS [40]. The proportion of women developing invasive cancer can, therefore, be expected to be higher in a population with a longer life expectancy, especially as the rate of progression appears to be higher in younger women.

The majority of women in the study underwent conventional core needle biopsy rather than vacuum-assisted biopsy for diagnosis. CNB is known to underestimate the coexistence of invasive disease in DCIS in approximately 20% of cases [25,41,42]. Nonetheless, the study still allows a ‘real world’ approach to the outcome of DCIS diagnosed predominantly at CNB to be determined. Finally, due to the relatively small number of subjects, multivariable analysis was not possible, thus confounding factors cannot be excluded.

Please cite this article in press as: Maxwell AJ, et al., Risk factors for the development of invasive cancer in unresected ductal carcinoma in situ, European Journal of Surgical Oncology (2018), https://doi.org/10.1016/j.ejso.2017.12.007

Conclusions

High cytonuclear grade of DCIS, mammographic microcalcification, young age and lack of endocrine therapy were significant risk factors for progression to invasive breast cancer after a median interval of 45 months in this group of women diagnosed with DCIS on needle biopsy but who did not undergo surgical resection for at least one year. These findings suggest that complete surgical excision of high grade DCIS should continue, as per current standard of care protocols. The natural history of low grade DCIS, however, remains uncertain. Whilst there are concerns about possible overtreatment of women with this condition, established management practice should not be changed in the absence of firm evidence, and the option of active surveillance for women with non-high grade DCIS should be offered within the context of a clinical trial.

Ethical approval

This study did not require ethical approval, as it is an audit using data obtained as part of usual patient care. UK cancer registries have approval under Section 251 of the UK National Health Service Act 2006 to collect all diagnostic and treatment information for cancer patients without the patient's implicit consent.

Funding

The study received no specific funding. The data were collated, maintained and quality assured by the Screening Quality Assurance Service and the National Cancer Registration and Analysis Service, which are part of Public Health England, a publicly funded executive agency of the UK Department of Health, established in 2013. Prior to this, the data were collected, maintained and quality assured by the publicly funded West Midlands Cancer Intelligence Unit.

DD is supported by the University of Oxford, Cancer Research UK (grant C8225/A21133), the Medical Research Council and the British Heart Foundation.

Conflicts of interest statement

The authors declare no conflicts of interest.

Acknowledgements

The authors would like to thank all the clinicians who submitted patient data.

Dr Elaine Harkness, Division of Informatics, Imaging & Data Sciences, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, UK provided valuable assistance with the statistical analysis.

The contributions of Mr Hugh M Bishop, former Steering Group Chair, and of Professor Adele Francis (now deceased) to this study are acknowledged.

This study has been accepted for poster presentation at the San Antonio Breast Cancer Symposium, December 2017.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejso.2017.12.007.

Appendix

Members of the Sloane Project Steering Group at the time of writing:
Professor Alastair Thompson (Chair of the Sloane Project Steering Group)
Professor of Surgery, University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA.
Mrs Karen Clements.
National Audit Project Senior QA Officer, Screening QA Service (Midlands and East), Public Health England, Birmingham, UK.
Dr Hilary Dobson.
Consultant Radiologist, West of Scotland Breast Screening Programme, Glasgow, UK.
Professor David Dodwell.
Professor of Clinical Oncology, St James's Institute of Oncology, Leeds, UK.
Professor Andrew Evans.
Professor of Breast Imaging, Ninewells Hospital and Medical School, Dundee, UK.
Professor Andrew Hanby.
Professor of Breast Cancer Pathology, St James's University Hospital, Leeds, UK.
Mrs Bridget Hilton.
National Audit Project Senior QA Officer, Screening QA Service (Midlands and East), Public Health England, Birmingham, UK.
Mrs Olive Kearins.
Head of QA, Screening QA Service (Midlands and East), Public Health England, Birmingham, UK.
Dr Gill Lawrence.
Specialist Audit Advisor, UK.
Dr Anthony Maxwell.
Consultant Radiologist, Nightingale Centre, Wythenshawe Hospital, Manchester, UK.
Professor Sarah Pinder.
Professor of Breast Pathology, Guys and St Thomas' Hospitals, London, UK.
Dr Elinor Sawyer.
BRC Clinical Research Consultant in Clinical Oncology, Guys Hospital, London, UK.
Mr Mark Sibbering.
Consultant Surgeon, Derby City General Hospital, Derby, UK.
Professor Valerie Speirs
Professor of Experimental Pathology and Oncology, Leeds Institute of Cancer and Pathology, University of Leeds, Leeds, UK.
Dr Jeremy Thomas.
Consultant Pathologist, Western General Hospital, Edinburgh, UK.
Professor Ian Tomlinson
Professor of Molecular and Population Genetics, Wellcome Trust Centre for Human Genetics, Oxford, UK.
Professor Graham Ball.
Reader in Bioinformatics, Nottingham Trent University, Nottingham, UK.
Dr Matthew Wallis.
Consultant Radiologist, Addenbrooke's Hospital, Cambridge, UK.
Ms Maggie Wilcox.
Patient Advocate, Independent Cancer Patients' Voice, UK.

References

[1] Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. JNCI J Natl Cancer Inst 2010;102(3):170–8.

[2] Independent UK Panel on breast cancer screening. The benefits and harms of breast cancer screening: an independent review. Lancet 2012;380(9855):1778–86.
[3] Narod SA, Iqbal J, Giannakeas V, Sopik V, Sun P. Breast cancer mortality after a diagnosis of ductal carcinoma in situ. JAMA Oncol 2015;1(7):888–96.
[4] Sagara Y, Mallory MA, Wong S, Aydogan F, DeSantis S, Barry WT, et al. Survival benefit of breast surgery for low-grade ductal carcinoma in situ. JAMA Surg 2015;150(8):739–45.
[5] Benson JR, Jatoi I, Toi M. Treatment of low-risk ductal carcinoma in situ: is nothing better than something? Lancet Oncol 2016;17(10):e442–51.
[6] Meyerson AF, Lessing JN, Itakura K, Hylton NM, Wolverton DE, Joe BN, et al. Outcome of long term active surveillance for estrogen receptor-positive ductal carcinoma in situ. Breast 2011;20(6):529–33.
[7] Ryser MD, Worni M, Turner EL, Marks JR, Durrett R, Hwang ES. Outcomes of active surveillance for ductal carcinoma in situ: a computational risk analysis. JNCI J Natl Cancer Inst 2016;108(5). djv372.
[8] Francis A, Thomas J, Fallowfield L, Wallis M, Bartlett JMS, Brookes C, et al. Addressing overtreatment of screen detected DCIS; the LORIS trial. Eur J Cancer 2015;51(16):2296–303.
[9] Patient-Centered Outcomes Research Institute. Comparison of operative versus medical endocrine therapy for low risk DCIS: the COMET trial. http://www.pcori.org/research-results/2016/comparison-operative-versus-medical-endocrine-therapy-low-risk-dcis-comet; 2016 [Accessed 18 May 2017].
[10] Elshof LE, Tryfonidis K, Slaets L, van Leeuwen-Stok AE, Skinner VP, Dif N, et al. Feasibility of a prospective, randomised, open-label, international multicentre, phase III, non-inferiority trial to assess the safety of active surveillance for low risk ductal carcinoma in situ - the LORD study. Eur J Cancer 2015;51(12):1497–510.
[11] Erbas B, Provenzano E, Armes J, Gertig D. The natural history of ductal carcinoma in situ of the breast: a review. Breast Cancer Res Treat 2006;97(2):135–44.
[12] Welch HG, Black WC. Using autopsy series to estimate the disease "reservoir" for ductal carcinoma in situ of the breast: how much more breast cancer can we find? Ann Intern Med 1997;127(11):1023–8.
[13] Worni M, Greenup RA, Mackey AM, Akushevich I. Trends in treatment patterns and outcomes for DCIS patients: a SEER population-based analysis. J Clin Oncol 2014;32(Suppl. 15):1007.
[14] Ozanne EM, Shieh Y, Barnes J, Bouzan C, Hwang ES, Esserman LJ. Characterizing the impact of 25 years of DCIS treatment. Breast Cancer Res Treat 2011;129(1):165–73.
[15] Wallis MG, Clements K, Kearins O, Ball G, Macartney J, Lawrence GM. The effect of DCIS grade on rate, type and time to recurrence after 15 years of follow-up of screen-detected DCIS. Br J Cancer 2012;106(10):1611–7.
[16] Vicini FA, Shaitelman S, Wilkinson JB, Shah C, Ye H, Kestin LL, et al. Long-term impact of young age at diagnosis on treatment outcome and patterns of failure in patients with ductal carcinoma in situ treated with breast-conserving therapy. Breast J 2013;19(4):365–73.
[17] Kong I, Narod SA, Taylor C, Paszat L, Saskin R, Nofech-Moses S, et al. Age at diagnosis predicts local recurrence in women treated with breast-conserving surgery and postoperative radiation therapy for ductal carcinoma in situ: a population-based outcomes analysis. Curr Oncol 2014;21(1):e96–104.
[18] Cronin PA, Olcese C, Patil S, Morrow M, Van Zee KJ. Impact of age on risk of recurrence of ductal carcinoma in situ: outcomes of 2996 women treated with breast-conserving surgery over 30 years. Ann Surg Oncol 2016;23(9):2816–24.
[19] Holmberg L, Wong YNS, Tabár L, Ringberg A, Karlsson P, Arnesson L-G, et al. Mammography casting-type calcification and risk of local recurrence in DCIS: analyses from a randomised study. Br J Cancer 2013;108(4):812–9.
[20] Thurfjell E, Thurfjell MG, Lindgren A. Mammographic finding as predictor of survival in 1-9 mm invasive breast cancers. Worse prognosis for cases presenting as calcifications alone. Breast Cancer Res Treat 2001;67(2):177–80.
[21] Tabar L, Chen H-HT, Yen MFA, Tot T, Tung T-H, Chen L-S, et al. Mammographic tumor features can predict long-term outcomes reliably in women with 1-14-mm invasive breast carcinoma. Cancer 2004;101(8):1745–59.
[22] Peacock C, Given-Wilson RM, Duffy SW. Mammographic casting-type calcification associated with small screen-detected invasive breast cancers: is this a reliable prognostic indicator? Clin Radiol 2004;59(2):165–70.
[23] James JJ, Evans AJ, Pinder SE, Macmillan RD, Wilson ARM, Ellis IO. Is the presence of mammographic comedo calcification really a prognostic factor for small screen-detected invasive breast cancers? Clin Radiol 2003;58(1):54–62.
[24] Evans AJ, James JJ, Pinder SE. Mammographic casting-type calcification associated with small screen-detected invasive breast cancers: is this a reliable prognostic indicator? Clin Radiol 2004;59(2):163–4.
[25] Brennan ME, Turner RM, Ciatto S, Marinovich ML, French JR, Macaskill P, et al. Ductal carcinoma in situ at core-needle biopsy: meta-analysis of underestimation and predictors of invasive breast cancer. Radiology 2011;260(1):119–28.
[26] Jakub JW, Murphy BL, Gonzalez AB, Conners AL, Henrichsen TL, Maimone S, et al. A validated nomogram to predict upstaging of ductal carcinoma in situ to invasive disease. Ann Surg Oncol 2017;24(10):2915–24.
[27] Cuzick J, Sestak I, Pinder SE, Ellis IO, Forsyth S, Bundred NJ, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol 2011;12(1):21–9.
[28] Fisher B, Dignam J, Wolmark N, Wickerham DL, Fisher ER, Mamounas E, et al. Tamoxifen in treatment of intraductal breast cancer: national Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet 1999;353(9169):1993–2000.
[29] Forbes JF, Sestak I, Howell A, Bonanni B, Bundred N, Levy C, et al. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in post-menopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. Lancet 2016;387(10021):866–73.
[30] Margolese RG, Cecchini RS, Julian TB, Ganz PA, Costantino JP, Vallow LA, et al. Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial. Lancet 2016;387(10021):849–56.
[31] Maxwell AJ, Hanson IM, Sutton CJ, Fitzgerald J, Pearson JM. A study of breast cancers detected in the incident round of the UK NHS breast screening programme: the importance of early detection and treatment of ductal carcinoma in situ. Breast 2001;10(5):392–8.
[32] Duffy SW, Dibden A, Michalopoulos D, Offman J, Parmar D, Jenkins J, et al. Screen detection of ductal carcinoma in situ and subsequent incidence of invasive interval breast cancers: a retrospective population-based study. Lancet Oncol 2016;17(1):109–14.
[33] Elston CW, Sloane JP, Amendoeira I, Apostolikas N, Bellocq JP, Bianchi S, et al. Causes of inconsistency in diagnosing and classifying intraductal proliferations of the breast. Eur J Cancer 2000;36(14):1769–72.
[34] Ellis IO, Coleman D, Wells C, Kodikara S, Paish EM, Moss S, al. Impact of a national external quality assessment scheme for breast pathology in the UK. J Clin Pathol 2006;59(2):138–45.
[35] Ernster VL, Barclay J, Kerlikowske K, Grady D, Henderson IC. Incidence of and treatment for ductal carcinoma in situ of the breast. JAMA 1996;275(12):913–8.
[36] Barnes NLP, Dimopoulos N, Williams KE, Howe M, Bundred NJ. The frequency of presentation and clinico-pathological characteristics of symptomatic versus screen detected ductal carcinoma in situ of the breast. Eur J Surg Oncol 2014;40(3):249–54.
[37] Roulson J, Benbow EW, Hasleton PS. Discrepancies between clinical and autopsy diagnosis and the value of post mortem histology; a meta-analysis and review. Histopathology 2005;47(6):551–9.
[38] Møller H, Richards S, Hanchett N, Riaz SP, Lüchtenborg M, Holmberg L, et al. Completeness of case ascertainment and survival time error in English cancer registries: impact on 1-year survival estimates. Br J Cancer 2011;105(1):170–6.
[39] Solin LJ, Kurtz J, Fourquet A, Amalric R, Recht A, Bornstein BA, et al. Fifteen-year results of breast-conserving surgery and definitive breast irradiation for the treatment of ductal carcinoma in situ of the breast. J Clin Oncol 1996;14(3):754–63.
[40] Early Breast Cancer Trialists' Collaborative Group EBCTCG. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst Monogr 2010;2010(41):162–77.
[41] Doebar SC, de Monye C, Stoop H, Rothbarth J, Willemsen SP, van Deurzen CHM. Ductal carcinoma in situ diagnosed by breast needle biopsy: predictors of invasion in the excision specimen. Breast 2016;27:15–21.
[42] Caswell-Smith P, Wall M. Ductal carcinoma in situ: is core needle biopsy ever enough? J Med Imaging Radiat Oncol 2017;61(1):29–33.

Please cite this article in press as: Maxwell AJ, et al., Risk factors for the development of invasive cancer in unresected ductal carcinoma in situ, European Journal of Surgical Oncology (2018), https://doi.org/10.1016/j.ejso.2017.12.007